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Pesticide Fact Sheet Number 3.2: Ethoprop

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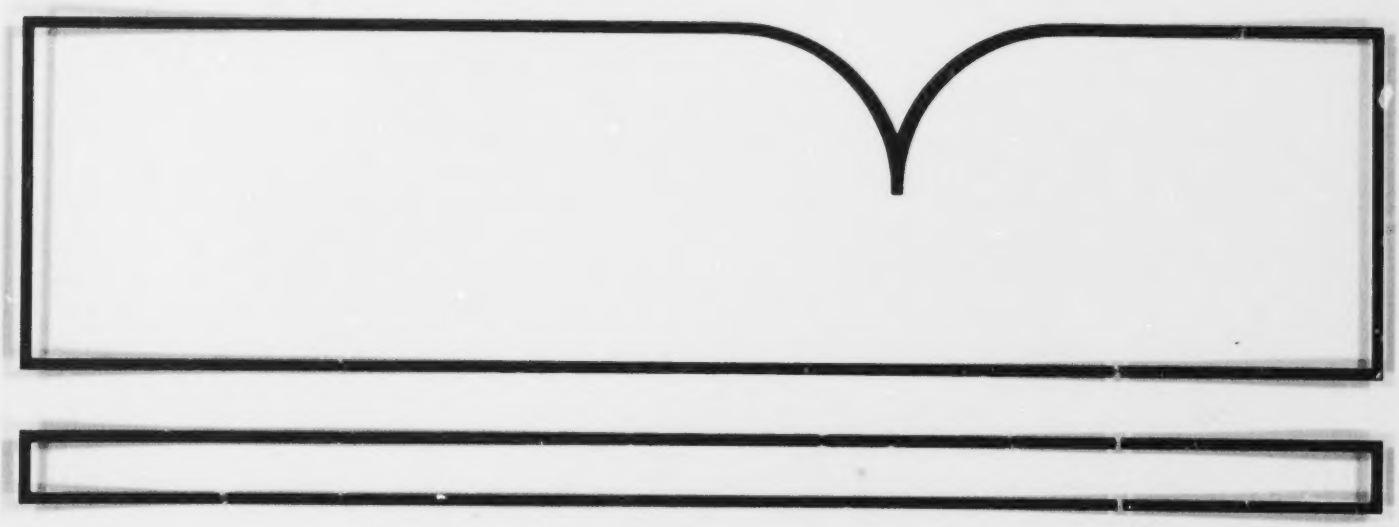

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This document contains up-to-date chemical information, including a summary of the Agency's regulatory position and rationale, on a specific pesticide or group of pesticides. A Fact Sheet is issued after one of the the following actions has occurred.

1. Issuance or reissuance of a registration standard,
2. Issuance of each special review document,
3. Registration of a significantly changed use pattern,
4. Registration of a new chemical, or
5. An immediate need for information to resolve controversial issues relating to a specific chemical or use pattern.

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Pesticides, regulations, Chemical Information Fact Sheet, Use Patterns, science findings.

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EPA

Pesticide Fact Sheet

Name of Chemical: ETHOPROP
Reason for Issuance: Registration Standard
Date Issued: June 30, 1988
Fact Sheet Number: 3.2

1. DESCRIPTION OF CHEMICAL

Generic Name: O-ethyl S,S - dipropyl phosphorodithioate

Common Name: Ethoprop

Empirical Formula: $C_8H_{19}O_2PS_2$

Trade Names: Mocap®, VC 9-104

EPA Pesticide Chemical (Shaughnessy) Number: 041101

Chemical Abstract Service Number (CAS): 13194-48-4

Pesticide Type: Insecticide, Nematocide, and Fungicide

Chemical Class: Organophosphate

U.S. Registrant: Rhone - Poulenc, Inc.

2. USE PATTERNS AND FORMULATIONS

Application Sites:

Food crop application of ethoprop: bananas, broccoli (EUP), cabbage, califlower (EUP), corn grain, corn fodder and forage, cucumbers, mushrooms, okra, fresh corn including sweet corn (kernals plus cob with husk removed), lima beans, lima bean foage, snap beans, snap bean forage, peanuts, peanut hay, pineapples, pineapple fodder and forage, potatoes, soybeans, soybean forage and hay, sugarcane, sugarcane fodder and forage, and sweet potatoes (40 CFR §180.31 and §180.262). There are no international tolerances or Codex Maximum Residue Limits for residues of ethoprop. The ethoprop tolerance (40 CFR §180.262) should be revised to read, "pineapples, pineapple fodder and forage," instead of "Pineapple fodder and forage."

3. SCIENCE FINDINGS

Summary Science Statement

Ethoprop is an organophosphate insecticide whose primary mechanism of toxicity is cholinesterase inhibition. Animal studies have shown that ethoprop inhibits plasma, erythrocyte, and brain cholinesterase activity. Technical ethoprop is highly toxic (Toxicity Category I to mammals when acutely administered orally, dermally, or via inhalation). Application of 0.1 ml of undiluted ethoprop (technical) into rabbit eyes for the eye irritation test produced 100% mortality within one hour post exposure (Toxicity Categroy I). No delayed neurotoxicity was observed in hens administered approximately 70% ethoprop.

Treatment-related inhibition of brain, erythrocyte, and plasma cholinesterase activities were observed in a rat subchronic feeding study (90 days). The pattern of cholinesterase inhibition suggested that the no observable effect level (NOEL) for cholinesterase depression was approximately 0.3 ppm (0.015 mg/kg/day). Cholinesterase inhibition (plasma and erythrocyte) was also judged to have occurred at the lowest dose tested (1.0 ppm).

The potential chronic toxicity, oncogenicity, teratology, and reproductive toxicity of ethoprop could not be fully evaluated with the available data (see pages 4,5,6 for the details) Additional information is required.

An acceptable battery of mutagenicty tests (gene mutation, chromosomal abberation, and DNA damage) was submitted. In the presence of a metabolic activation system, ethoprop was determined to be a genotoxic agent *in vitro* in two types of chromosomal aberration studies. Ethoprop was not determined to be a mutagen in two gene mutations studies. For DNA damage, an assay determined ethoprop to be inactive (negative).

Four special studies are required to address certain questions which arose in the assessment of the ethoprop database. The first is designed to determine a NOEL for cholinesterase inhibition in the rat, the second to resolve issues in the dog chronic feeding study (including the determination of a NOEL for cholinesterase inhibition in the dog), the third to confirm *in vitro* genotoxic findings with an *in vivo* cytogenic assay, and the fourth to resolve the issue of eye lesions noted in the mouse oncogenicity study.

The Agency is unable to provide a quantitative estimate of the ethoprop potential for groundwater contamination. Ethoprop was found to be very mobile in columns of loam soil types. Additional studies are required to assess the potential for groundwater contamination including hydrolysis, photolysis in water and soils, leaching of soil degradates, and field dissipation.

Chemical/Physical Characteristics Of Ethoprop (Technical)

- °Clear yellow tinted liquid with a strong mercaptan odor.
- °Boiling point 86-91°C at 0.2 mm Hg.
- °Solubility in water to 843 ppm at 21°C and soluble in most organic solvents.
- °No corrosion observed on SAE type 1020 steel or aluminum foil of the type used to line a bag of granular formulation 332 hours at 21°C.

Toxicological Characteristics

Acute Oral Toxicity: Toxicity Category I [LD50 (mg/kg; rats): males, 61.03 (49.19-75.01)];females, 32.8 (25.41-42.44).

Acute Dermal Toxicity: Toxicity Category I [LD50 (mg/kg; rabbits): 25.7 (14.44-45.83) mg/kg].

Acute Inhalation: Toxicity Category I [LC50 (mg/l; rats): 0.12 (0.08-0.17)].

Primary Dermal Irritation: Toxicity Category I. All rabbits died within 8 hours post exposure. No primary irritation index was obtainable.

Primary Eye Irritation: Toxicity Categroy I. All rabbits died within one hour post exposure.

Skin Sensitization: Data was not submitted, and not required because of the early onset of death observed in the other acute tests.

Delayed Neurotoxicity: No acute delayed neurotoxicity was observed in the hen. The oral LD50 (hens) of Mocap EC is 9.9 (8.8-12.1) mg/kg

Subchronic Dermal Toxicity: The study reviewed was considered supplementary because large variations exhisted in plasma and erythrocyte cholinesterase levels observed among the animals on test. An acceptable study is required.

Subchronic Feeding Studies: (Non-rodent) - An acceptable 13-week study was conducted using the beagle dog. Ethoprop (technical) was tested using dietary dose levels of 1.0, 3.0, and 100 ppm. Cholinesterase inhibition was the only treatment related effect noted. No toxicological significant inhibition of plasma or erythrocyte cholinesterase was judged to have occurred at the lowest dose tested (1.0 ppm; 0.075 mg/kg/day). The lowest effect level for cholinesterase depression was 3.0 ppm (0.225 mg/kg/day).

(Rodent) - The subchronic feeding study (rats; Charles River) is considered supplemental, and has been used to establish a provisional acceptable daily intake (PADI). Three groups of 25 albino rats per sex were fed ethoprop technical in the daily diet at doses of 0, 0.3, 1.0 or 100 ppm for 90 days. The pattern of cholinesterase inhibition suggests that the NOEL is approximately 0.3 ppm (0.015 mg/kg/day). A new subchronic rat study is not required provided an acceptable rat chronic feeding study is conducted. The data obtained from the chronic study will suffice in this case for the information needed for a subchronic oral toxicity study.

Chronic Toxicity

Due to various deficiences, the available studies for nonrodent and rodent chronic toxicity do not fulfill current requirements. Adequate data are needed. Beagle dogs were fed ethoprop in their diets at 0, 0.025, 1.0 and 10 mg/kg/day for 52 weeks. Plasma cholinesterase (ChE) was inhibited in females at all dose levels. Whereas, the mid- and high dose levels are effect levels for erythrocyte ChE inhibition, and the high-dose is an effect level for brain ChE inhibition. Also, all male dogs at all dose levels exhibited less weight gain than the control group. No NOEL could be determined from the study.

In order to determine a NOEL for plasma erythrocyte and and the issue of decreased male body weight gain in all test groups, the Agency is requiring an abbreviated study of 17 weeks.

In the chronic feeding study, Fisher 344 rats were fed 0, 4.5, 9.0 and 18 ppm of ethroprop for 12 weeks, and then placed on diets of 0, 49, 98 or 196 ppms for the remaining 52 weeks. Cholinesterase inhibition was observed at all the dose levels and a NOEl could not be determined. The MTD was considered to be the highest dose tested. The study is considered supplemental, and additional information is required.

The one year dog chronic feeding study is evaluated to be inadequate, but does not need to be repeated. The Agency

is requiring specified special studies to resolve the deficiencies noted in the one-year dog chronic feeding study. The Agency review for chronic and oncogenic potential in rats (MRID 00138636) indicated that for the chronic feeding portion of this study the classification was core - supplemental. It cannot be upgraded since no NOEL for cholinesterase inhibition was observed. At all doses of ethoprop tested, cholinesterase inhibition of >20% was observed. Additional information must be submitted. In addition, the Agency is requiring summary incidence tables for clinical observations.

Oncogenicity

The requirements for oncognicity testing (two species) are not fulfilled, and data must be submitted. B6C3F1 mice were fed 0, 15, 30, and 60 ppm of ethoprop in their diet for 78 weeks. The study did not demonstrate oncoginic effects under the conditions of this study. However, the highest dose tested (60 ppm) is considered to be at least two times under the maximum tolerated dose. This study is considered supplemental.

Fisher 344 rats were fed 0. 4.5, 9.0, and 18 ppm of ethoprop for 12 weeks, and then placed on diets containing 0, 49, 98, or 196 ppm of ethoprop for the remaining 52 weeks. Under the conditions of this study, there was an increase in the number of C-cell adenomas of the thyroid in males receiving the high-dose when compared to controls, and there was a dose-related increase in the number of endometrial polyps in females. However, the total number of individual tissues examined histologically per group was not presented. Consequently, the incidence of these lesions cannot be determined or analyzed statistically, and an evaluation of the oncogenic potential of ethoprop cannot be performed from the reported study. This study is considered by the Agency to be supplementary. Additional data are required.

Teratology

Ethoprop technical was adminstered by oral intubation to groups of Sprague-Dawley rats at doses of 0. 0.16, 1.6, and 16.0 mg/kg/day (MRID 00104532). However, based on the data presented and the current guidelines for examining teratology studies, the potential of the test material to cause developmental toxicity cannot be fully evaluated. More specifically, certain deficienceis were noted in the rat study at the time the initial registration standard was prepared (although occurrances of compound-related terata were not). At that time, a request was made for historical control data with regard to parameters such as delayed ossification. Apparently, these data were not submitted. Since then, new Agency guidelines have stressed that observations be made for all aspects of developmental toxicity, and not just occurrances of terata. For these reasons,

complete historical control data for all measured fetal and maternal parameters (details in MRID 00104532) and individual litter data for all measured fetal parameters are now required. The issue of potential developmental toxicity in the rat needs to be addressed before the status of the study (now supplemental) can be upgraded.

A teratology study in New Zealand White rabbits was submitted in which ethoprop technical was administered by gavage to groups of animals at doses of 0, 0.125, 0.500, and 2.00 mg/kg. Since the data submitted in the study were not sufficient to fully evaluate such things as whether test material adminstration resulted in maternal toxicity or resulted in an increase in skeletal variations, a NOEL and LEL for maternal and developmental toxicity could not be determined. Additional data, including historical control data for fetal and maternal parameters, are needed for the resolution of these issues (MRID 00161619).

Reproduction

A three-generation study in Fisher 344 rats in which ethoprop technical was administered at dose levels of 0, 60.5, 131, and 262 ppm was not sufficient to satisfy the data requirements for reproductive toxicity (MRID 00162164). The data presented was considered insufficient to determine a NOEL and LEL for maternal and developmenal toxicity, because questions were raised with regard to such things as culling procedures and the appropriateness of other parts of the protocol, animal illness, lack of food consumption and diet analysis data, inadeqate data presentation, and descrepancies in data reporting.

Mutagenicity: An acceptable battery of mutagenic tests (gene mutation, negative; chromosomal abberation, positive; and DNA damage, inactive) were evaluated. An acceptable bone marrow cytogenetic analysis in rats is needed to provide *in vitro* confirmation of *in vitro* findings in the chromosomal abberation studies submitted.

Metabolism: Available studies do not fulfil the requirement for metabolism data. However in one study the metabolites O-ethyl-S-propylphosphorothioic acid and O-ethyl-phosphoric acid, as well as ethoprop, were detected in the urine. An acceptable study is required.

Special Studies: The following special studies are required to address questions generated from the evaluation of the submitted data:

A special study is required in rats for the purpose of determining a definitive NOEL for plasma, erythrocyte, and brain cholinesterase inhibition. A protocol must be submitted to the Agency for approval prior to commencement of this study.

A subchronic feeding study in dogs is required to address issues of decrease in animal body weight gain and the lack of a NOEL for cholinesterase inhibition in the present 1-year study. This study is required for purposes of determining a most sensitive species for cholinesterase inhibition. A protocol must be submitted to the Agency prior to initiation of this study.

An acceptable rat bone marrow cytogenetic analysis study is required for *in vivo* confirmation of *in vitro* cytogenetic findings observed in the chromosomal aberration studies.

Two 60-day mouse studies are required in order to resolve the question of whether eye lesions observed in the 78-week mouse oncogeniciy study were systemic effects of the test material administration. One test must be by oral gavage in the B6C3F1 mouse, and the other one must be a dietary study in another mouse strain.

Environmental Characteristics

Data on the metabolism of ethoprop in plants are not considered adequate. These data identified several metabolites of ethoprop, but did not quantitate them. Given the nature of this chemical, unusual or exceptionally toxic metabolites are not expected. Quantitation of known and/or supposed metabolites will allow a more complete toxicological evaluation. Additional data form ^{14}C-radiolableled experiments on corn, potatoes, and cabbage are needed. Although not required previously, metabolism studies on ruminants and poultry are now needed to elucidate the pathway for metabolism of ethoprop in animals. Tolerances for ethoprop are currently expressed in terms of parent compound *per se*, and will be reassessed when the additional required studies are submitted and reviewed.

The Agency is unable to provide a quantitative estimation of the ethoprop potential for groundwater contamination. Ethoprop was found to be very mobile in columns of loamy sand and loam soil types. Additional studies are required to assess the potential for ground water contamination including hydrolysis, photolysis in water and soils, leaching of soil degradates, and field dissipation.

Ecological Characteristics

Birds

Ethoprop technical is highly toxic to bird species on acute oral, dietary, and dermal bases. Acceptable acute and subchronic dietary toxicity studies are available. Field dissipation studies which will more accurately define acute hazards to bird species inhabiting treated areas are required. Avian reproduction studies may be needed if it is found that ethoprop residues remain at significant levels in the field for an extended period of time. Acute and simulated field studies show sufficient hazard to wildlife to require the following field studies: 1) One study with the emulsifiable concentrate on pineapples. 2) One study with the granular product (G) on corn or potatoes.

-Ring-neck pheasants; 95% a.i.; oral LD50 = 118 (103-134 mg/kg).
-Bobwhite quail; 95% a.i.; oral LD50 = 33 (27-40 mg/kg).
-Mallards; LC50 = 287 (215-382 mg/kg).

Aquatic Studies

Technical ethoprop is very highly toxic to aquatic invertebrates. It is moderately to highly toxic to rainbow trout and highly toxic to bluegills, crustaceans, and marine fish species. Ethoprop is slightly toxic to embryo larvae of oyster species. Further assessment to the potential hazards to aquatic organisms cannot be made until certain environmental fate data are submitted and reviewed. At that time an estimated environmental concentration (EEC) will be developed. Further aquatic data requirements will be reserved until the EEC and environmental fate data are available.

- Rainbow trout; 95% a.i.; LC50 = 1.02 (0.56-2.10) mg/l.
- Bluegills; 95% a.i.; LC50 = 0.30 (0.23-0.40 mg/l).
- Mysidopsis bahai (shrimp); LC50 = 23 ppb.
- Callinectes sapidus (blue crabs); 100% mortality at 24 hours when exposed to 1 ppm.
- Cyprinidon varieatus (sheepshead minnows); LC50 (static tank; 96 hours testing) = 748.3 ppb.
- Leiostomus xanthurus (spot); LC50 (static tank; 96 hours testing) = 32 ppb.
- Cyprinidon varieatus (sheepshead minnows); flow thru

tank; 96 hours testing; LC50 = 232.67 ppb.
- Lagodon rhomboides (pinfish); flow thru tank; 96 hours testing; LC50 = 7.2 ppb.
- Oyster species (embryo larvae); 95% a.i.; EC50 = 11.0 5.6-32 ppm).

Tolerance Assessment

Tolerances for residues of ethoprop in or on food commodities are published in 40 CFR §180.262 and §180.31. The tolerances are set at 0.02 ppm for all the listed commodities. A conclusive tolerance reassessment was not made at this time due to lack of data for the following: a) The metabolism of ethoprop in plants and animals. b) Storage stability. c) Residue and toxicity studies. Additional data are required. A final reevaluation of the tolerances and ADI will be made as soon as the requested data concerning storage stability, metabolism, residue, and toxicitiy are reevaluated. No new tolerances for ethoprop will be granted in the interim.

Data on the metabolism of ethoprop in plants are not considered adequate. These data indentified several plant metabolites of ethoprop, but did not quantitate them. Given the nature of this chemical, unusual or exceptionally toxic metabolites are not expected. Quantitation of known and/or supposed metabolites will allow a more complete toxicological evaluation. Additional data from ^{14}C-radiolabled experiments on corn, potatoes, and cabbage are needed. Although not required previously, metabolsim studies on ruminants and poultry are now needed to eludidate the pathway for metabolism of ethoprop in animals. Tolerances for ethoprop are currently expressed in terms of parent compound per se, and will be reassessed when the additional required studies are submitted and reviewed.

Adequate analytical methodologies are available for en forcement of the present tolerances in terms of ethoprop per se. Ethoprop is completely recovered by the multiresidue procedures in the Pesticide Analytical Manual (Vol. 1, protocols II and III), and partially recovered by protocol I. No data are available for protocol IV. These data are required. If any metabolites of toxicological concern are identified in the metabolism studies required, additional validated analytical methodologies may be needed.

4. SUMMARY OF REGULATORY POSITIONS AND RATONALES

- Ethoprop meets the criteria for resticted use classification.
- Ethoprop is not a candiate for Special Review at this time.
- The Agency will not grant any new tolerances or new uses for ethoprop until data required under this Standard have been received and tolerances reassessed.

- The Agency is unable to provide a quantitative estimation of the ethoprop potential for groundwater contamination. Additional studies required are hydrolyis, photolysis in water and soil, leaching of soil degradates, and field dissipation.
- In order to remain in compliance, updated label precautions are required to address the hazard to fish and wildlife.
- The Agency will reevaluate reentry protection for ethoprop when the requested data are received and evaluated. In the interim, 24 hours is the established reentry interval for all crops.

5. SUMMARY OF REQUIRED LABEL MODIFICATION

An updated Environmental Hazard Statement is required.

6. SUMMARY OF OUTSTANDING DATA REQUIREMENTS

Data Gaps

The Agency has identified missing data required to fully evaluate the human and environmental risks associated wih the use of ethoprop.

Toxicology	Time Frame for Data Submission (Months)
°21 day dermal toxicity (rabbit)	12
°90 day feeding (rodent; not required if a chronic rat feeding study is performed).	15
°Chronic toxicity (rodent and nonrodent)	50
°Oncogenicity (mouse, rat)	50
°Teratogenicity (rat, rabbit)	15
°Reproduction (2-generation rat)	39
°Mutagenicity testing (cytogenetic analysis)	14
°Metabolism	24
°Other Special testing	
rat	14
subchronic	18
subchronic (2)	24

Environmental Fate/Exposure

°Hydrolysis	9
°Leaching and adsorption/desorption	12
°Soil dissipation	27
°Soil dissipation, long term	50
°Spray drift	27

°Photogegradation in air, soil, and water..... 9
°Volatility (lab).....12
°Volatility (field).....15
°Rotational crops (confined; accumulation).....39
°Rotational crops (field; accumulation).....50
°Accumulation: fish.....12

Fish & Wildlife

°Actual field testing with birds.....48

Residue Chemistry

°Nature of residue (metabolism, plants, and livestock).....18
°Residue analytical methods.....15
°Storage stability data.....18
°Magnitude of residue in meat, milk, poultry, and eggs.....15
°Residue data.....15-30

Product Chemistry

°All purity and composition..... 6
°Analysis and certification of product.....12
°Physical and chemical characteristics; i.e. color, physical state, odor, boiling point, dissociation constant, stability..... 6
°All analysis and certification of product ingredients.....12

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